Serological Response to Early Measles Vaccination

by Sushil John, G. Lalitha, Kuryan George and Abraham Joseph
Community Health Department, Christian Medical College, Vellore, Tamil Nadu, India

Summary
This study compares the persistence of measles IgG antibody in 239 children vaccinated at 6–8 months of age with 76 children vaccinated after 8 months of age. Among the children vaccinated prior to 9 months, 49 per cent of the children between 16 and 44 months and 33 per cent of children over 54 months had levels of measles IgG antibody conventionally considered protective. Among the children older than 48 months, 67 per cent of children vaccinated before 9 months and 13 per cent of children vaccinated after 8 months had antibody levels below the conventionally accepted protective levels of 0.2 IU/ml. Older children had lower antibody levels than younger children.

Measles immunization before 9 months with the standard titer Edmonston–Zagreb vaccine has not provided a large proportion of under-five children with protective levels of measles IgG antibody. A significant proportion of children vaccinated at the currently recommended age also had suboptimal levels. It is difficult to protect the majority of the measles-susceptible population with a single dose regardless of the immunization schedule used. A second dose of measles vaccine may be necessary to increase the herd immunity.

Introduction
The Community Health Department of the Christian Medical College, Vellore, India has been offering a single dose of standard titer measles vaccine to infants from 6 months of age since 1986. The vaccine efficacy in those vaccinated at 6–8 months was comparable with those vaccinated after 8 months. However, in March 1999, there was an outbreak of measles in three villages of the programme area of the Community Health Department. This was the first major outbreak of measles since 1986 in this area, which had a high coverage with the measles vaccine for over 10 years.

Accumulation of susceptible children in the older age groups, because of primary vaccine failures due to the early administration of measles vaccine or waning immunity among children vaccinated early in infancy, could generate secondary cases among susceptible younger siblings, with consequent morbidity and mortality in this vulnerable group. In order to test the above hypothesis, we estimated the persistence of antibodies to measles in children vaccinated at 6–8 months of age and compared them with antibody persistence in those vaccinated after 8 months of age.

Materials and Methods
The Community Health Department of the Christian Medical College, Vellore, India has established an integrated Community Health and Development (CHAD) programme in the Kaniyambadi area. A detailed description of the CHAD programme and its health information system is reported elsewhere. The measles vaccine coverage in this block was 68 per cent in 1985, 79 per cent in 1988, and over 90 per cent since 1990.

Methodology of the study
This paper represents data from two separate studies. In the first study 239 children vaccinated between 6 and 8 months were chosen. Among the children vaccinated at 6–8 months, 82 were 16–19 months, 79 were 37–44 months, and 78 were 54–61 months of age at the time of study.

Three windows were chosen: one at 15–17 months, to look at status before the first booster; the next around nursery school entry at 3 years; and the last just before 5 years. Villages were chosen by simple random sampling. Once a village was chosen, all eligible children vaccinated between 6 and 8 months were included in the study. In a separate study, 76 children who had received measles vaccine between 9 and 11 months and who were 49–60 months old at the time of the study were enrolled from all the villages of the Kaniyambadi area. In all, 315 children were enrolled.

Any child who had history of an exanthematous fever or received more than one dose of measles vaccine was excluded from the study. The parents of
the selected children were contacted at home and informed consent was obtained. The date of measles vaccine was reconfirmed from the home-based immunization card. The height and weight were measured. The nutritional status was determined using the Indian Academy of Paediatrics (IAP) classification.

Socioeconomic status (SES) was evaluated on a three-point scale depending on the type of house, the occupation of the head of the household, and the highest education in the family. The scores for all three points were added up to obtain the SES scores. The scores were classified into low, middle, and high based on the percentile distribution. The scores below the 25th percentile were considered low, between the 25th and 75th percentiles as middle, and those above the 75th percentile as high.

A sample of blood was obtained from each child by venupuncture. The blood was transferred to labeled test tubes and transported to the laboratory within 4 hours. In the laboratory, serum was separated, placed in pro-vials and stored at –30°C until it was tested. Serum IgG levels were estimated by enzyme-linked immunosorbent assay (ELISA) using the SERION ELISA classic measles-IgG virus quantitative kit manufactured be Serion Immunodiagnostics GmbH of Wurzburg, Germany. IgG levels were interpreted according to the manufacturer’s instructions, as follows: <0.15 U/ml, not protective; 0.15–0.2 U/ml, doubtful; >0.2 U/ml, protective.

The data entry and analysis was done using Epi-Info version 6.04.

### Results

Among the children vaccinated at 6–8 months, 118 were boys and 121 girls. The proportion of subjects with protective measles antibody at the time of the study is shown in Table 1. The proportion of children with protective measles antibody at 54–61 months was lower than on the younger age groups ($\chi^2 = 7.93$, $p = 0.018$). The geometric mean titre (GMT) of antibody was not significantly different in the three age groups (Table 2). Among the children vaccinated after 8 months of age, 39 were girls and 37 boys. A total of 86.8 per cent of them had protective levels of measles IgG. This proportion was significantly higher than those vaccinated at 6–8 months ($\chi^2 = 45.82$, $p = 0.00$) (Table 3). There was no significant difference in the proportion of children with protective level of IgG by nutritional status, socioeconomic status, or gender.

### Discussion

The EPI recommendation to vaccinate against measles at or after 9 months of age is a compromise between achieving reasonably high seroconversion rates and the need to protect susceptible infants. In the Kaniyambadi area, however, we have been administering measles vaccine starting at 6 months of age, based on locally available immunogenicity data.6 Subsequent studies confirmed the efficacy of the measles vaccine administered at this age.1 Moreover, there were no epidemics of measles in this community for over a decade since the introduction of this strategy. However, in 1999 an outbreak of measles within this community that predominantly affected children over 5 years of age, prompted us to re-examine this strategy by determining the persistence of protective antibodies following measles vaccination. This study showed that among children older than 4 years, 67 per cent of those vaccinated at 6–8 months did not have protective antibody levels compared with 13 per cent vaccinated at 9–11 months. A lack of protective antibodies among

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Measles IgG levels (IU/ml)</th>
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<tbody>
<tr>
<td>16–19</td>
<td>29 (35.4) 13 (15.9) 40 (48.8) 82 (100)</td>
</tr>
<tr>
<td>37–44</td>
<td>29 (36.4) 11 (13.9) 39 (49.4) 79 (100)</td>
</tr>
<tr>
<td>54–61</td>
<td>43 (55.1) 9 (11.5) 26 (33.3) 78 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>101 (42.3) 33 (13.8) 105 (43.9) 239 (100)</td>
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</tbody>
</table>

Figures in parentheses indicate %.

Comparing those currently 54 months and older with the rest $\chi^2 = 7.93$, $p = 0.018$.

### Table 2

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Geometric mean titre (IU/ml)</th>
</tr>
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<tbody>
<tr>
<td>16–19</td>
<td>0.23 (0.18–0.28)</td>
</tr>
<tr>
<td>37–44</td>
<td>0.27 (0.19–0.35)</td>
</tr>
<tr>
<td>54–61</td>
<td>0.24 (0.17–0.34)</td>
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### Table 3

<table>
<thead>
<tr>
<th>Age at measles vaccination (months)</th>
<th>Measles IgG levels (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>43 (55.1) 9 (11.5) 26 (33.3) 78 (100)</td>
</tr>
<tr>
<td>0.15–0.2</td>
<td>5 (6.6) 5 (6.6) 66 (86.8) 76 (100)</td>
</tr>
<tr>
<td>&gt;0.2</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>78 (100)</td>
</tr>
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Comparing the proportion with protective levels by age at vaccination $\chi^2 = 45.82$, $p = 0.00$.

10 fmh009 (ad/k) 27/4/04 8:53 am Page 176

S. JOHN ET AL.
children older than 4 years who were vaccinated at 6–8 months of age may be responsible for outbreaks of measles among schoolchildren. Since the proportion lacking protective antibody levels at 54 months and above were significantly higher than those aged 16–53 months, it may be deduced that waning antibody levels amongst those who seroconverted after vaccination at 6–8 months partly contributed to this phenomenon. Similar findings have also been reported from West Africa.

Although these children lacked protective antibody levels, it is likely that lower antibody levels offer some degree of protection. The West African study showed that the measles in older immunized children was milder, with almost no mortality. Thus, the strategy of vaccinating early seems to increase the mean age of occurrence and reduce measles morbidity and mortality. On the other hand, clinical measles among schoolchildren could generate secondary cases among susceptible younger siblings with consequent morbidity and mortality in this vulnerable group. The study also showed that 13 per cent of children among those vaccinated at 9–11 months did not show optimum levels of measles antibodies. It is likely that in the absence of exposure to natural infection there would be a further loss in antibody and increasing susceptibility to measles with age. This suggests that in a highly immunized population, control of measles will be difficult to achieve with a single dose, regardless of the immunization schedule used. It is possible that two doses of measles vaccine, by improving individual protection and herd immunity, could prevent the early cases as well as the later vaccine failures, and consequently reduce the costs of controlling measles outbreaks by reducing the number of outbreaks. However, careful consideration needs to be given to the timing of the second dose of the vaccine to obtain the maximum benefit. The factors that need to be considered are the pattern of waning immunity and decreasing vaccine coverage with increasing age in most EPI programmes. A few questions need to be answered before any further decisions can be made on measles control strategies that would prevent the early cases and provide more long-lasting immunity.

- Would a second dose of measles successfully protect the children who do not currently have protective levels of IgG after one dose? Will the immunity produced be long lasting?
- The girl child of today is the mother of tomorrow. Would low antibody levels in women vaccinated early in childhood lead to earlier loss of maternal antibodies in their children and make those infants susceptible even earlier?

References